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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/558,472	04/25/00	BRISTOW M	MYOG:004DIV1

HM12/0511

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1632	5

DATE MAILED: 05/11/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/558,472	BRISTOW ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 17-23 is/are pending in the application.

4a) Of the above claim(s) 17-22 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 23 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

Election/Restrictions

I. Claims 17-22, drawn to a method of treating myocardial failure using an agent that is a protein, classified in class 514, subclass 44, for example.

II. Claim 23, drawn to a method of treating myocardial failure using a transgene, classified in class 514, subclass 2, for example.

These inventions are distinct, each from the other because of the following reasons:

Invention I is distinct from Invention II because the method in Invention I is materially distinct from the method in Invention II, as each method is directed to products (protein and transgene) which differ considerably in structure and function, and in technical and therapeutic considerations. In addition, the transgene in the method of Invention II is not required for use of the protein in the method of Invention I.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one

or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

During a telephone conversation with Steven Highlander on 10/24/00, a provisional election was made without traverse to prosecute the invention of Group II, claim 23. Affirmation of this election must be made by applicant in replying to this Office action. Claims 17-22 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

The preliminary amendment, filed on 4/25/00, has been entered.

Claims 17-23 are pending.

Claims 17-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claim 23 is under current examination.

Priority

The priority data, on page 1 of the specification, should be updated to indicate that Application Serial No. 09/016,075 is now abandoned.

Abstract

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 250 words. It is important that the abstract not exceed 250 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract is objected to because it is not limited to a single paragraph and it exceeds 25 lines of text. See 37 CFR 1.72(b) and MPEP § 608.01(b).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 23 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is directed to a method for treating myocardial failure in a human, comprising administering an effective amount of an agent that directly causes an increase in the quantity of α-myosin heavy chain (α-MHC) in the myocardial tissue of the heart (claim 17). In particular, the elected agent is a transgene encoding α-MHC (claim 23).

The specification discloses a method of myocardial gene therapy to increase α-MHC expression by delivering a transgene encoding α-MHC to a human so that the α-MHC transgene is expressed in the myocardial tissue of the heart (see p. 14, lines 20-28 of the instant application). The specification further discusses construction of the transgene (p.15 of the instant application) and modes of delivery of the transgene (p, 16, lines 4-15 of the instant application). The specification specifically teaches up-regulation of α-MHC mRNA in myocardial tissue in human subjects suffering from cardiomyopathy, who received medical treatment with β-blocking agents (see example 5, of the instant application). However, an increase in the amount of α-MHC mRNA in myocardial tissue does not provide a prediction of gene therapy for any subject having myocardial failure. Additionally, the specification fails to provide a correlation to therapeutic levels of expression of α-MHC transgenes in an *in vivo* setting in any subject having myocardial failure. Furthermore, the specification fails to teach or provide guidance for what level of α-MHC expression would provide a therapeutic effect in a human with myocardial failure, or how to measure the therapeutic effect in such a subject.

Numerous factors complicate *in vivo* gene transfer and expression, which result in therapeutic effects. See Eck and Wilson ('Gene-Based Therapy' in The Pharmocological Basis of Therapeutics, 1996), who report that numerous factors complicate *in vivo* gene therapy with respect to predictably achieving levels and duration of gene expression which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume distribution,

rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. See page 82, column 1, first paragraph. These factors differ dramatically based on the vector used, the route of administration of the vector, the protein being produced, which cells are the target cells, and the disease and/or host being treated. It is further noted that Eck and Wilson support the importance of tailoring a gene therapy vector and method to specific diseases and/or disorders. See page 82, column 1, first paragraph.

The specification fails to teach the level of α-MHC transgene expression in myocardial tissue necessary to achieve treatment of myocardial failure in a human subject. Moreover, the specification fails to address how to overcome any of the above unpredictable parameters in the gene therapy art such that one would be able to achieve therapeutic α-MHC transgene expression in target cells in a human subject with myocardial failure. It is important to note that treatment encompasses complete amelioration of symptoms associated with myocardial failure or cure of myocardial failure; it is not clear that the mere expression of an α-MHC transgene within myocardial tissue is sufficient to provide therapy in a subject with myocardial failure.

Claim 23 reads on targeting, as is consistent with the disclosed modes of delivery. While progress has been made in recent years for gene transfer *in vivo*,

vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate that a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles

for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

As such, with respect to the unpredictable nature of the gene therapy art in general and in particular, when taken with the specification's lack of any teaching of, or sufficient guidance for, α-MHC transgene expression *in vivo*, it is not predictable if α-MHC transgene expression in myocardial tissue would be considered to be therapeutic in a human subject with myocardial failure, since somatic gene delivery often results in only limited expression in inadequate numbers of cells.

Prior to the time of filing, Nabel (*Circulation*, 1995; pp. 1-17) teaches that, "Despite substantial progress, a number of technical issues need to be addressed before gene therapy is applied safely and broadly to cardiovascular diseases." (see p. 1, *Introduction*, 3rd line). Nabel further teaches that the goals of development of cardiovascular gene therapy depend on technical advances in the development of methods of gene delivery, long-term, highly-efficient and targeted expression to relevant cells, and vectors that are safe for human administration. (see p. 1, bottom of page, p. 2, top of page). Nabel further teaches that myocardial gene therapy has been hindered by limited transfection efficiency, transient expression of recombinant genes, and vectors that have provoked inflammatory responses (see p. 5-6, *Myocyte Gene Transfer*).

Additionally, Hajjar (*Circulation Research*, 2000; pp. 1-12) teaches that, "bridging the gap between [these] basic investigative studies and clinical gene therapy remains a formidable task." (See p. 1, *Abstract*, lines 10-11). Hajjar further teaches that relatively

few vectors exist which achieve high-level transgene expression in post-mitotic cells, such as cardiomyocytes, and that these vectors evoke a robust immune response (see p. 2, 2nd paragraph, lines 4-7). Because of this immune response, Hajjar states that clinical applications will require other vectors or further refined vectors. (see p. 3, 1st paragraph, lines 5-7). Hajjar further teaches that, "It is important to acknowledge that the field of gene therapy has not yet proven its clinical value in any context." (seep. 2, 3rd line from the bottom) and that, "Optimizing conditions for gene transfer into large animals and eventually humans will require substantial further investigation." (see p. 4, 1st paragraph, last sentence).

Note that the cited post-filing art clearly indicates the unpredictable status of the gene therapy art, in a general sense, as well as how it specifically pertains to myocardial gene therapy. Accordingly, in view of the quantity of experimentation necessary to determine the parameters listed above for achieving myocardial gene therapy, the lack of direction or guidance provided by the specification to carry out myocardial gene therapy, the absence of working examples for the demonstration or correlation to achieving therapeutic α-MHC gene expression *in vivo*, and the unpredictable and undeveloped state of the art with respect to the gene therapy art, as well as to myocardial gene therapy for *in vivo* function, it would have required undue experimentation for one skilled in the art to carry out the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 depends from a non-elected claim, Claim 17. For examination purposes, claim 23 is being interpreted to fully encompass claim 17. Claim 23 should be amended to read only on the elected invention.

As claim 17 is fully encompassed within claim 23, claim 17 is incomplete, which renders the claim indefinite. There is no period at the end of the claim. It is further unclear how the step of the method, "administering an effective amount of an agent that directly causes an increase in the quantity of α-MHC in the myocardial tissue of the heart," correlates to the intended effect of the method (the preamble), "treating myocardial failure" since, in light of specification, mere administration of an α-MHC transgene would not be sufficient to achieve treatment of myocardial failure without the expression of the recombinant DNA. Amendment to claim 23 is requested.

Conclusion

Claim 23 appears to be free of the cited prior art of record, because the cited prior art fails to teach or suggest treatment of a human with myocardial failure via α-MHC gene therapy. However, these claims are subject to other restrictions.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (703) 305-1019. Should the examiner be unavailable, inquiries should be directed to Karen Hauda, Supervisory Primary Examiner of Art Unit 1632, at (703) 6608. Any administrative or procedural questions should be directed to Patsy Zimmerman, Patent Analyst, at (703) 305-2758. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-7401.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

TNT

Thaian N. Ton
Patent Examiner
Group 1632

JILL D. MARTIN
PRIMARY EXAMINER